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(54) Title: TREATMENT OF RESPIRATORY DISTRESS SYNDROME WITH POWDER SURFACTANT COMPOSITION

(57) Abstract: The condition of "wet lung", in which there is slow and incomplete clearance of lung fluid, often as a pulmonary complication following inter alia sepsis, trauma and shock, is treated by administering to the respiratory system a powdered surface active phospholipid (SAPL) composition, preferably comprising a mixture of phosphatidyl choline (PC) and phosphatidyl glycerol (PG).

TREATMENT OF RESPIRATORY DISTRESS SYNDROME WITH POWDER SURFACTANT COMPOSITION

This invention relates to the treatment of wet lung in mammals, particularly in humans. Wet lung is a condition in which, in simplistic terms, the lungs are flooded with water, more specifically a condition involving infiltration of fluid from ultrafiltrate of plasma, in conjunction with other fluids, i.e. water, and in which there is slow or incomplete clearance of lung fluid. Clinical symptoms include transient tachypnea, expiratory grunting, substernal retraction and mild cyanosis, caused as a result of fetal lung fluid. Wet lung can occur in a number of pulmonary disorders.

Wet lung frequently occurs, for example, in premature babies, and also occurs in infants delivered via caeserean or a precipitous delivery, developing within the first 6 hours of life. About two percent of babies are hypoxic at birth and are immediately placed on a ventilator which inflates their lungs with oxygen-enriched air through an endotracheal tube. In many cases, the hypoxia is relieved by this procedure. However, in a substantial number of cases, the babies remain blue and are mostly then diagnosed as suffering from respiratory distress syndrome (RDS) which is believed to be caused by a deficiency of surfactant on the lungs.

These babies are traditionally treated by instillation of a single dose of exogenous surfactant dispersed in a sterile aqueous medium and, with this treatment, the hypoxia is often relieved within a minute or two. The popular explanation for this effect is that the surfactant reduces the surface tension at the liquid/air interface within the lungs, thus reducing the effort required for inflating the lungs and stimulating expansion of the lungs.

Whereas surfactant rescue of this kind has reduced infant mortality substantially, there are still a number of babies who do not thrive after these combined treatments. The Applicants believe that this initial relief of hypoxia is not the whole answer and that there is an important second stage to surfactant rescue. It is now thought that this second stage is related to the retention of water by the lungs as evidenced by the

cloudy X-rays and decreased pulmonary compliance of babies who cannot be weaned from the ventilator until these factors are resolved. It is believed that this problem comes down to one major factor, i.e. retained water, since lung compliance is highly dependent on fluid content.

A similar condition occurs in adults with acute respiratory distress syndrome (ARDS), which develops as a pulmonary complication of a variety of disorders, such as sepsis, trauma and shock. Others include SIRS, prolonged hypotension, lung contusion, fat embolism, pancreatitis, multiple emergency transfusions, post cardiopulmonary bypass, burn injury, and disseminated intravascular coagulation.

Wet lung has also been observed in servicemen who have been exposed to the shock wave from exploding mines and artillery shells. There have been many recorded cases of soldiers dying several hours after an artillery barrage due to flooded lungs. In all cases of wet lung, the patient exhibits continued breathing difficulties, even when nursed on a ventilator.

ARDS is also found in both children and adults in cases of near drowning.

The present invention is based on the appreciation that administration of a surface-active phospholipid (SAPL) to the respiratory system in a manner and in a sufficient amount to form and maintain a coating of the SAPL on the alveolar surface of the lung provides a solution to the problem of wet lung, and enables the patients to recover from this condition, thereby providing a long-term solution to their breathing problems.

There are a number of surface-active lipid compositions on the market, but most of these are solvent extracts from bovine or porcine lungs. As a result, they are expensive and run the risk of transmitting pathogens or pirogues of animal origin to the patient. All of these compositions are currently administered 'wet', i.e. the surfactant is dispersed in saline and given as either a bolus or as a droplets from a nebulizer.

The present invention starts from the viewpoint that it is not good practice to be adding more water to a flooded lung.

For these reasons, this invention proposes to treat wet lung using a dry, preferably synthetic, SAPL powder composition, and delivering it dry.

Most suitably the dry SAPL composition is prepared from phosphatidyl choline (PC) and phosphatidyl glycerol (PG), but the invention is not limited solely to use of these lipids. Natural endogenous materials contain neutral lipids, fats, inorganic ions etc, all of which are integral to their form and function, and inclusion of these in formulations for use in the invention is not excluded. Preferred SAPL compositions are synthetic dipalmitoyl phosphatidyl choline (DPPC) co-precipitated from a common solvent system with PG in the weight ratio of 6:4 to 8:2, especially about 7:3. The composition is advantageously administered to the respiratory system as a dry powder since it spreads extremely rapidly on water.

The phospholipids used in accordance with the invention have acyl substituents on the phosphatidyl groups. As in their natural counterparts, the acyl groups may comprise identical or different, saturated or unsaturated acyl radicals, generally C14-22, especially C16-20, acyl radicals. Thus the phospholipids may comprise, by way of acyl radicals, the saturated radicals palmitoyl C16:0 and stearoyl C18:0 and/or the unsaturated radicals oleoyls C18:1 and C18:2 . Diacyl substitution is preferred and the phospholipids used in the compositions in accordance with the invention more particularly comprise two identical saturated acyl radicals, especially dipalmitoyl and distearoyl, or a mixture of phospholipids in which such radicals predominate, in particular mixtures in which dipalmitoyl is the major diacyl component. Thus PC and PG may be used may be used with the same diacylphosphatidyl profile as in PC and PG extracted from human or animal or vegetable sources, but if synthetic sources are used the dipalmitoyl component may predominate, as in the DPPC mentioned above.

As also mentioned above, the SAPL compositions are most preferably protein free, but in some circumstances the presence of proteins and adjuvants, especially naturally occurring materials from plant or animal sources, or synthetically derived, may be tolerated, especially proteins associated with PC and PG *in vivo* in conjunction with a dry powdered formulation for use in this invention. For example the presence of apoproteins C and D in conjunction with may be tolerated in SAPL compositions for human use.

DPPC can be prepared synthetically by acylation of glycerylphosphorylcholine using the method of Baer & Bachrea -Can. J. of Biochem. Physiol 1959. 37, page 953 and is available commercially from Sigma (London) Ltd. The PG may be prepared from egg phosphatidyl-choline by the methods of Comfurions et al. Biochem. Biophys Acta 1977,488, pages 36 to 42; and Dawson, Biochem J. 1967,102, pages 205 to 210, or from other phosphatidyl cholines, such as soy lecithin.

When co-precipitated with DPPC from a common solvent such as chloroform, PG forms with DPPC a fine powder which spreads rapidly over the surfaces of the airways and lungs. The most preferred composition of the invention contains DPPC and a phosphatidyl glycerol derived from egg phosphatidyl choline, which results in a mixture of C16, C18 (saturated and unsaturated) and C20 (unsaturated) acyl groups.

While not wishing to be limited to the following theory it is believed that, when absorbed (reversibly bound) to the alveolar wall, SAPL provides a semi-permeable membrane enabling the concentration gradient of ions generated by ion-channel pumps to actually shift water by osmosis from the surfaces of the alveolar wall. The known deficiency of SAPL which occurs in RDS could lead to a deficiency in this absorbed semi-permeable lining and would, in turn, compromise the ability to pump water. This situation should be corrected by administering exogenous SAPL in a form which displays two properties. First it spreads rapidly over the surface of the incumbent fluid for widespread distribution throughout the lung. Secondly, it then absorbs to the

epithelial surface to repair /fortify the semi-permeable barrier comprising similar material.

The above theory is supported by the following experiments which have been carried out using DPPC and blends of DPPC and PG in solid, powder form.

In a first experiment, a blend of DPPC and PG in the weight ratio of 7:3 DPPC: PG was deposited on a sheet of filter paper and heated to normal blood temperature (about 37°C). A semipermeable membrane was formed on the filter paper which was capable of establishing a gradient of solids (in this case glucose) and enabled water to be shifted by osmosis from the side of the treated paper to the other.

Although the honeycomb structure of aveoli makes it difficult to conduct absorption studies, it was then demonstrated in studies using radio-labelled DPPC that this SAPL will absorb to bronchial epithelium and that PG potentates this absorption by a factor of 2~3. A mixture of 7:3 DPPC:PG provides essentially optimal absorption levels.

Once having attained the condition described above, one of the factors which will reduce the life of the lining or coating of SAPL will be the presence of enzymes such as phospholipase capable of digesting DPPC and/or PG. Such enzymes only attack the laevo-rotatory form which constitutes a naturally occurring form. Accordingly, it is preferred that the SAPLs used in the present invention preferably contain the dextro-rotatory form or at least comprise the racemic mixture which is obtained by synthetic routes.

The SAPL compositions preferably used in accordance with the present invention are finely-divided, solid powders and are described in detail in our co-pending PCT applications WO 99/27920 and WO 00/30654, the whole contents of which are incorporated by reference. However in summary, our above applications indicate that an important feature of the SAPL compositions that are usable in the present invention is that they are in the form of a powder, that is, it is in solid form. The "dry" surfactant

has a high surface activity. Preferably, the SAPL composition has two components. Suitably the first component of the SAPL comprises one or more compounds selected from the group consisting of diacyl phosphatidyl cholines. Examples of suitable diacyl phosphatidyl cholines (DAPCs), are dioleyl phosphatidyl choline (DOPC); distearyl phosphatidyl choline (DSPC) and dipalmitoyl phosphatidyl choline (DPPC). Most preferably, the first component is DPPC.

The second component may comprise one or more compounds selected from the group consisting of phosphatidyl glycerols (PG); phosphatidyl ethanolamines (PE); phosphatidyl serines (PS); phosphatidyl inositols (PI) and chlorestyl palmitate (CP).

Phosphatidyl glycerol (PG) is a preferred second component. PG is also a preferred second component because of its ability to form with the first component, especially PC and particularly DPPC, a very finely-divided, dry powder dispersion in air.

The composition advantageously comprises a diacyl phosphatidyl choline and a phosphatidyl glycerol. The phosphatidyl glycerol is advantageously a diacyl phosphatidyl glycerol. The acyl groups of the phosphatidyl glycerol, which may be the same or different, are advantageously each fatty acid acyl groups which may have from 14 to 22 carbon atoms. In practice, the phosphatidyl glycerol component may be a mixture of phosphatidyl glycerols containing different acyl groups. The phosphatidyl glycerol is expediently obtained by synthesis from purified lecithin, and the composition of the acyl substituents is then dependent on the source of the lecithin used as the raw material. It is preferred for at least a proportion of the fatty acid acyl groups of the phosphatidyl glycerol to be unsaturated fatty acid residues, for example, mono-or di-unsaturated C18 or C20 fatty acid residues.

Preferred acyl substituents in the phosphatidyl glycerol component are palmitoyl, oleoyl, linoleoyl, linolenoyl and arachidonoyl. The medicament preferably comprises dipalmitoyl phosphatidyl choline and phosphatidyl glycerol, with the phosphatidyl

moiety of the phosphatidyl glycerol advantageously being obtainable from the phosphatidyl moiety of egg lecithin.

The compositions are administered preferably in a dry, finely-divided state, using a delivery device such as described in our above co-pending applications, or by directly introducing the aerosolised powder, e.g. by an endotracheal tube, into the lungs. The dosage and/or period of administration should be long enough to maintain a layer over the surface of the lung for a sufficient time for the patient to recover from the wet lung syndrome. The conditions of the patient's lungs and the recovery from the wet lung condition can be detected by X-ray or other imaging of the lungs at intervals, e.g. after administration of sequential amounts of the SAPL.

The particle size of the SAPL should be sufficiently small to reach the lungs when introduced into the subject's airways, e.g. in the form of an aerosolised powder. Generally, the particle size should be less than 10 micron, preferably less than 5 micron e.g. 2-4 micron. Aerosolised powder of this later size range can be introduced via an endotracheal tube having a 2~3 mm diameter. By this technique a fine particle dose of about 25~50mg can be successfully introduced into the lungs.

"Finely divided" as used herein means that the material has a particle size distribution which is such that at least a major proportion by weight of the particles are small enough to enter into a patient's airways and, preferably, deep into the lungs when inhaled. In practice, the first and second components preferably each have a particle size distribution which is such that not less than 90%, by weight, of the particles of those components in combination, and more preferably of each of the first and second components, have a particle size of not greater than 10μm, and especially of not greater than 5μm. Advantageously, the median particle size of the combined first and second components, and more preferably of each of the first and second components is not more than 10μm, and preferably not more than 5μm. The median particle size may be less than 3μm, for example, about 1.2μm. It may be desirable in some circumstances for the particles to have a median particle size of at least 0.5μm (especially if the

material is co-administered with other ingredients/actives in bi, ternary, or quarternary mixtures that are hygroscopic). The size of the particles may be calculated by laser diffraction, or by any other method by which the aerodynamic diameter of particles can be determined. "Median particle size" as used herein means mass median aerodynamic diameter (MMAD). The MMAD may be determined using any suitable method, for example, using a Multi-Stage Liquid Impinger in accordance with the method described in European Pharmacopoeia (supplement 1999) 2.9.18 (Aerodynamic assessment of fine particles). Alternatively, the size distribution of the particles may be characterised by their volume mean diameter (VMD). Advantageously, the VMD is not more than 10μm, for example not more than 5μm, and preferably less than 3μm. Finely divided dry powders of this kind (which may be described as fumed powders) can be adsorbed onto the surfaces of lung tissue and are believed, in use, to become bound to the epithelium.

To obtain a mixture in which the particle size is suitable for use in the device of the invention, the phospholipid components may be dissolved in a suitable solvent, for example ethanol, the solution filtered and vacuum-dried, and the solid product size-reduced to obtain particles of the desired size. During size-reduction, care should be taken to protect the mixture from moisture, oxygen, direct heat, electrostatic charge and microbial contamination.

Other forms of particle / powder production include, e.g. lyophillisation, spray drying, SEDS, etc., all of which will alter the intrinsic properties and may impart crystallinity. Depending on the method of production, the particle size acceptance limits, may change from those indicated above. For example depending on the route of manufacture, e.g. co-precipitation followed by lyophilisation, densities of the final product may be considerably less than that of an alternative method, e.g. spray drying. In this instance the effective MMAD, which is dependent upon the product of the VMD and the square root of the ratios of the densities of a unit sphere, as compared to that of the sphere/particle in question, results in a large particle effectively having a smaller size due to said effect.

CLAIMS:

1. Use of a surface active phospholipid (SAPL) in the manufacture of a powder medicament for the treatment of wet lung in mammals.

2. Use according to claim 1 in which the medicament is a dry, finely-divided solid which is a blend of a first component consisting of one or more phosphatidyl cholines and a second component selected from one or more phosphatidyl glycerols, phosphatidyl ethanolamines, phosphatidyl serines, phosphatidyl inositols, and chlorestyl palmitate.

3. Use according to claim 1 in which the medicament is a dry, finely-divided solid which is a blend of phosphatidyl choline (PC) and phosphatidyl glycerol (PG).

4. Use according to claim 2 or 3, in which the phosphatidyl choline (PC) is dipalmitoylphosphatidyl choline (DPPC) or a mixture of phosphatidyl cholines in which DPPC is the predominant component.

5. Use according to claim 4 in which the SAPL comprises a blend of PC or DPPC and PG in which the weight ratio of PC or DPPC to PG is from 6:4 to 8:2.

6. Use according to claim 5 in which the ratio is about 7:3.

7. Use according to any one of the preceding claims in which the SAPL(s) are prepared synthetically.

8. Use according to any one of the preceding claims in which the PC, DPPC and/or PG comprise the dextro-rotatory form.

9. A method of treating wet lung in mammals which comprises administering to the respiratory system of a mammal suffering from wet lung, a dry powdered surface

active phospholipid (SAPL) composition in a sufficient amount and for a sufficient period to form and maintain a coating of the SAPL on the alveolar surfaces of the lungs.

10. A method according to claim 9 which includes imaging the patient's lungs after administration of the SAPL.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/GB 01/04761

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/685 A61K9/00 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, PAJ, MEDLINE, EMBASE, PASCAL, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MORLEY C J ET AL: "DRY ARTIFICIAL LUNG SURFACTANT AND ITS EFFECT ON VERY PREMATURE BABIES" LANCET, vol. 1, no. 8211, 1981, pages 64-68, XP001057977 page 64, column 2, paragraph 3 -page 65, column 1, paragraph 1 page 65 ---	1-10
X	MORLEY C J: "Prophylactic treatment of premature babies with artificial surfactant (ALEC)." DEVELOPMENTAL PHARMACOLOGY AND THERAPEUTICS, (1989) 13 (2-4) 182-3. , XP001062114 page 182, column 1, paragraph 1 ---	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance
'E' earlier document but published on or after the international filing date
'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
'O' document referring to an oral disclosure, use, exhibition or other means
'P' document published prior to the international filing date but later than the priority date claimed
'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Laffargue-Haak, T

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	ROBERTSON B ET AL: "Principles of surfactant replacement" BIOCHIMICA ET BIOPHYSICA ACTA. MOLECULAR BASIS OF DISEASE, AMSTERDAM, NL, vol. 1408, no. 2-3, 19 November 1998 (1998-11-19), pages 346-361, XP004276815 ISSN: 0925-4439 * see in particular p. 352, 2.4 Modes of surfactant administration * ---	1-10
A	WO 99 27920 A (HILLS BRIAN ANDREW ;WOODCOCK DEREK ALAN (GB); BRITANNIA PHARMACEUT) 10 June 1999 (1999-06-10) cited in the application -----	

INTERNATIONAL SEARCH REPORT

[redacted]mation on patent family members

Intern[redacted]pplication No
PCT/G[redacted]01/04761

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9927920 A	10-06-1999	AU 1251999 A	16-06-1999
		EP 1082108 A2	14-03-2001
		WO 9927920 A2	10-06-1999
		GB 2331925 A	09-06-1999